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Gazerani, Parisa

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Review

Epigenetics of Sleep Disruption

Parisa Gazerani *

Laboratory of Molecular Pharmacology, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, 9220 Aalborg East, Denmark; E-Mail: gazerani@hst.aau.dk

* **Correspondence:** Parisa Gazerani; E-Mail: gazerani@hst.aau.dk

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Abstract

Sleep plays an important role in maintaining brain function, memory consolidation, hormonal balance, immune system function, growth, and repair. The physiological and psychological effects of disruptions in sleep highlight its importance in human health and wellness. Epigenetic roles are proposed in sleep, and circadian regulation, but only a limited number of studies have determined the mechanism that underlies the epigenetics of environmental factors interacting with the sleep, particularly the ones related to sleep disruption. Therefore, studying epigenetics of sleep and sleep disorders can help elucidate the way these factors promote or inhibit sleep disorders, potentially guiding the development of precision medicines or preventive strategies. However, before discovering useful epigenetic-based interventions for sleep disorders, we need to overcome many challenges. As a relatively new field, there are unmet needs that call for further investigation of epigenetic mechanisms underlying sleep disruption. This review focuses on the current status of epigenetic mechanisms in sleep disruption (e.g., sleep deprivation and circadian dysregulation), which highlights a great potential of both animal and human studies to explain the disturbances in sleep, associated consequences, and novel therapeutic potentials. Translating the epigenetic research in sleep disturbances can eventually lead to better diagnosis, prognosis, prevention, and therapy in the clinics.

Keywords
Epigenetics; sleep; sleep deprivation; DNA methylation; acetylation; LncRNAs, miRNAs; epigenome-wide association studies

1. Sleep

Sleep is regulated by homeostatic and circadian mechanisms and is a reversible state. During sleep, a low sensory response with motor immobility is observed throughout the animal kingdom, with only a few exemptions [1]. It is defined as a fundamental element of life, with many studies collectively demonstrating its essential role in health. Several theories are merged to explain the function of sleep in decreasing the energy demands [2], restoring cellular processes [3], maintaining immune health [4], and regulating the communication between neurons [5]. Neuronal-based studies have highlighted the significant role of sleep in memory consolidation [6]. Achieving good sleep quality (e.g., low sleep latency, low number of awakenings, low waking after sleep onset, and better sleep efficiency) [7] and duration [8, 9] is necessary for overall health and well-being. Poor sleep is linked to a diverse range of health issues, including developmental impairments, somatic and cognitive deficits, and rapid aging. Sleep plays a multidimensional role in one's physiological and psychosocial aspects of life and is affected by a diverse range of internal and external parameters. Cellular mechanisms underlying the sleep function are being elucidated gradually. In humans, sleep diversity exists between the individuals and also within an individual in their life span, which proposes the role of genetic variations among individuals. However, environmental and lifestyle factors also contribute to this diversity.

Sleep in mammals consists of cycles of rapid eye movement (REM) and different stages of non-REM (NREM), which reflect the cortical activity patterns and can be monitored by electroencephalography (EEG). During sleep, a coordinated neural activity is seen in the hippocampus [10], where certain patterns of interactions are observed between CA1 pyramidal neurons and inhibitory interneurons [11]. It is proposed that the coordination between hippocampal and extra-hippocampal oscillatory activity during sleep promotes memory consolidation that is formed during wakefulness [12]. Sleep-wake cycles are regulated by the circadian clock, which is the master pacemaker in the suprachiasmatic nucleus that coordinates complex physiological processes and behaviors with the circadian rhythmicity [13]. Circadian rhythm is derived from the 24 h day and night (light-dark) cycle that accompanies biological cycles, including fasting-feeding, body temperature, hormone secretion, and sleep-wake. Also, both the internal feedback loop and the external environment interact with the circadian rhythms. Several chronotypes (preferred time of day for daily activities) exist while the two extreme preferences are termed as morningness and eveningness [14, 15], and these two chronotypes are reported to have genetic components [16, 17], i.e., they express two circadian clock-regulated genes *Per3* and *Nr1d2*. Ingram et al. in 2016 [16] measured the expression of *Per3* and *Nr1d2* in hair follicle samples and assigned the RNA chronotypes- morningness and eveningness to the participants. A difference was identified between these two groups even in decision-making tasks, where only a 3-hour phase difference in molecular clockwork was sufficient to influence the decision-making, highlighting the effects of endogenous clock function in human performance [16]. Chronotype

influences both physical and mental health [18, 19] with cortisol levels also being different in early and late hours preferring people. Early chronotype presents with a more pronounced adreno-cortical activation after waking up compared to the late chronotype [14]. Disruption in cortisol and melatonin rhythms [20] are known to impair circadian rhythms and play roles in disorders associated with sleep [21, 22], impaired glucose tolerance, or low level of alertness [23]. Polymorphisms and mutations of circadian genes were identified and reported with evidence highlighting the transcription of circadian clock genes being epigenetically regulated by the changes in DNA methylation, histone modifications, and structural chromatin alterations [24]. Most of the epigenetic modifications are driven by the external environment and lifestyle. Lack of sleep and sleep disturbances are common around the globe [25, 26]. For example, at least 7 h of sleep per night is recommended for adults, but the data reports that more than 30% of adults in the United States have an insufficient sleep [27]. In Finland, a similar trend was reported with one-third of the adult population experiencing sleep difficulties [28], where 25% reported a sleep of 6 h or less per night [26, 28] and up to 45.3% were affected by insomnia symptoms, according to a previous study [28]. Shift work, for example, night shift and an early morning shift, is a common reason for insufficient sleep. Working in shift leads to misalignment in circadian rhythms, homeostasis imbalance, and shortened sleep time by 1 to 4 h [29]. Indeed, shift work disorder (SWD) [30] is a medical condition characterized by complaints of excessive sleepiness or insomnia, accompanied by a reduction in sleep duration with over one-third of shift workers suffering from this condition [31, 32]. Epidemiological evidence shows that disrupted sleep contributes to several health issues [33], specifically in the aging societies, including type 2 diabetes [34], cardiovascular diseases, neurodegeneration, depression, cognitive, and emotional dysfunction [35]. Sleep disruption can either be a single acute disruption, repeated disruptions, or even a lifetime disruption [36]. Therefore, sleep must be looked upon as an important state that has a multifaceted influence on health and well-being [37] and all aspects of sleep must be taken into account such as duration, timing, pattern, and quality because they can affect cellular structure, gene expression, metabolic and hormone regulation, mood, alertness, and quality and longevity of life. Over the last decade, attempts have been made for a better understanding of underlying mechanisms that determine the consequences of sleep disruption and experimental studies are conducted in both laboratory animals and humans to address the unanswered questions in the field. The study designs are now modified to include different modalities, describing the consequences and mechanisms of sleep loss under the chronic sleep disruption, which mirrors the current condition of many modern societies. Models for continuous, intermittent, or stage-dependent sleep deprivation are applied for partial or total sleep deprivation (TSD) in animals and humans [37-39]. Advancing technologies have now permitted the identification of mechanisms underlying sleep disturbances and its multidimensional consequences such as the effect on brain cells, circuits, and metabolism shifts. However, several areas are still open for investigation, such as the activation mechanism of compensation or rescue and also questions about whether and how the adaptation occurs and failing of some processes in this regard [37].

The growing literature shows that insufficient sleep promotes epigenetic modifications and both acute and chronic sleep deprivation produces broad changes in epigenetic markers and patterns of gene transcription in animals [40-43] and humans [44, 45]. Targeting epigenetic factors have been challenging for many health conditions, such as cancer, psychiatric disorders, and

neurodegenerative diseases. Therefore, these strategies could ultimately result in future interventions to prevent or treat sleep disruptions.

2. Epigenetics of Sleep

The term "*epigenetic*" means "*in addition to changes in genetics*" and this includes any process that alters gene activity without changing the DNA sequence. Epigenetic theory mainly focuses on the interaction between the environment and gene expression. Epigenetic markers such as genomic imprinting, DNA methylation, histone modifications, and non-coding RNAs were identified in several human health conditions and related disorders [46-49]. Although epigenetic modifications can be transmitted from parents to their offspring [50, 51], maintaining itself through the generations [52, 53], some changes do reverse. DNA methylation and histone modification [54] make direct structural modifications influencing the gene expression. In contrast, non-coding RNAs are transcribed from DNA but not translated into protein. These functional RNA molecules regulate gene expression at the transcriptional and post-transcriptional levels [54]. miRNAs are emerging as diagnostic biomarkers in many human disorders, such as sleep apnea [55], neurodegenerative disorders [56], and pain [57-59].

DNA methylation is studied extensively in cancer [60] with first reports [61] highlighting the alterations of DNA methylation occurring throughout the genome of various cancer tissues compared to the normal tissues. The majority of these cancer-linked alterations were demonstrated by hypomethylation [62], but gradually it became evident that hypermethylation [63] also occurred in many cancers. Biological significance and clinical relevance of DNA methylation are increasingly being notified in cancer [64] and conditions such as aging [65] or even other disorders, namely, neurodegenerative and cerebrovascular disorders [66].

Besides DNA methylation [67], chromatin, a complex of histones, proteins, and DNA tightly bundled into the nucleus, can also be modified [68] by acetylation, enzymes, and some forms of RNA, such as microRNAs and small interfering RNAs [69]. After the modification, chromatin structure is altered, influencing the gene expression [70].

Another form of epigenetic inheritance is genomic imprinting, which is known in mammals, plants, and insects [71] and is defined as the regulation of a gene or chromosomal region depending on the sex of the transmitting parent [71]. The imprinted genes in the mammals are expressed in the parent-of-origin in a specific manner, playing an important role in the embryonic and extraembryonic growth and development and some human diseases, such as Beckwith-Wiedemann syndrome (BWS) and Russell-Silver syndrome (RSS) [72].

In the generation and regulation of the sleep-wake cycle, a complex interaction exists between neuroanatomical, neurochemical, neurophysiological, and genetic endogenous elements [73]. It is known that the environment plays a major role in the life of mammals and determines their developmental, physiological, or behavioral changes. It was proposed that external factors (e.g., light, darkness, diet, noise, heat, cold [74]), through the epigenetic mechanisms, might also contribute to circadian controlling of sleep and potentially be linked to sleep disturbances or disorders [75, 76].

Since the epigenetic mechanisms underlying the circadian regulation and sleep disorders is a broad-spectrum topic falling beyond the purpose of this review, we have mainly presented the epigenetic mechanisms underlying sleep disruption. We refer the readers to delve into excellent

reviews available in the literature if interested in genetics and epigenetics of circadian regulation and sleep disorders, such as sleep apnea [77-80].

2.1 Examples of Epigenetic Alterations in Sleep Deprivation

We still have a limited understanding of epigenetic factors, onset, and underlying mechanisms in sleep-wake disturbances, sleep disorders, and associated chronobiological disturbances [13]. It is proposed that epigenetics and sleep are interrelated, but we still do not know if connections are causal, modulatory, or correlative [81]. Hence, several hypotheses have emerged [13], where epigenetic pathways directly cause sleep-wake disorders by deregulating the circadian clock. Insomnia and excessive sleepiness are the most common sleep disturbances [82, 83], with literature indicating epigenetics to be related to these conditions [45, 84]. DNA methylation, histone modifications, and chromatin remodeling are regulated by the circadian clock [13, 85]. A review article [86] has also presented the epigenetic markers of sleep deprivation from the findings of animal and human studies.

2.1.1 DNA methylation

The addition of a methyl group to a cytosine-guanine dinucleotide (CpG) is termed as DNA methylation and is one of the epigenetic modifications. Many studies have provided evidence that DNA methylation is affected by sleep [13, 42, 86-88]. Massart et al. [42] demonstrated that acute sleep deprivation in mice resulted in a remarkable expression of *Dnmt3a1* and *Dnmt3a2 genes*. Narwade et al. [41] analyzed the transcriptome and reported altered expression of memory and neurotransmission associated genes in rats deprived of REM sleep. Another study has shown that twins with different diurnal preferences presented different DNA methylation patterns [84]. DNA methylation patterns are also found to be different in 52 genes in individuals who sleep less than 6.8 h (short sleepers) compared to those who sleep more than 7.8 h (long sleepers) [89]. In 2011, Zhu et al. [90] reported hypermethylation of cryptochrome circadian clock 2 (*CRY2*) and hypomethylation of *CLOCK* in the long-term night-shift workers. Four years later, Cedernaes et al. [88] reported the occurrence of DNA methylation following one night of sleep deprivation in men. The results from this study showed that CpG sites in period circadian clock 1 (*PER1*) and *CRY1* promoter were significantly hypermethylated in adipose tissue samples obtained from sleep-deprived men. However, no difference was found in gene expression, proposing a potential gap time following the DNA methylation, which can be explained by the potential requirement for more changes. For example, the contribution of several CpG sites or other mechanisms such as histone modifications or contribution of non-coding RNAs [88]. Nilsson et al., in 2016 [45] performed a genome-wide DNA methylation study and found that 269 probes were significantly altered in blood samples of sleep-deprived healthy men and to identify the potential genes with altered expression and DNA methylation changes following the sleep deprivation, the authors of this study correlated their results with Möller-Levet et al. [91]. The correlation showed that one CpG site with decreased DNA methylation in the Inhibitor of growth 5 (*ING5*) gene correlated to a similar decrease in expression of *ING5* [45].

These studies demonstrate that changes in DNA methylation occur in response to sleep deprivation and can help identify the epigenetic pathways affected by sleep loss. Further

investigations are required to define the patterns of sleep-specific DNA methylation and its consequences [86].

2.1.2 Histone Modification

Histones can be modified [92] by methylation on lysine or arginine residue, but the methylation is mostly observed in histone tails H3 and H4 at lysine residue. Histone methylation can be associated with either transcriptional repression or activation, depending on the position of the residues modified and the number of methyl groups. Histone methylation is mediated by chromatin remodelers, including histone methyltransferases, histone lysine demethylases (KDMs), and other histone-modifying enzymes. Histone methylation and demethylation play an important modulatory role in the chromatin restructuring and RNA transcription, hence, controlling a diverse range of biological processes [92]. For example, studies have suggested that compounds such as 3-deazaneplanocin A (DZNep) inhibit histone trimethylation of lysine 27 on histone H3 and lysine 20 on histone H4. DZNep is shown to control the sleep-wake cycle and release sleep-related neurochemicals via the histone methylation process [93].

Histone can also be acetylated by the enzyme histone acetyl-transferase (HAT), while deacetylation reactions are handled by histone deacetylase (HDAC). Histone acetylation reduces the interaction between histone and DNA, leading to the loosened chromatin conformation, which further facilitates transcriptional events. Histone acetylation is required in the regulatory process of gene expression, and it is shown that maintenance of circadian rhythm and sleep homeostasis is modulated by circadian genes, where the gene expression is regulated by histone modifications. Disrupted sleep homeostasis was reported in the mice models lacking in circadian genes [94], and since sleep deprivation alters the circadian gene expression, histone modification can be one of the potential underlying mechanisms. However, only a few studies have looked into histone acetylation after the occurrence of sleep deprivation. Duan et al. [40] analyzed the samples of the hippocampus from sleep-deprived rats and identified reduced acetylated histones at BDNF promoter IV. This observation was consistent with a previous study by Guzman-Marin et al. [95], who showed a reduced BDNF transcription and translation following prolonged sleep deprivation state. Future studies are required to identify the epigenetic markers present on the chromatin that are altered by sleep loss [86], eventually leading to the identification of sleep-specific biomarkers and targeting sleep loss disorders.

2.1.3 Non-Coding RNAs

As their name suggests, non-coding RNAs are the molecules that are transcribed from DNA but do not code for proteins. Several types of non-coding RNAs exist that are classified into two large groups based on their size: long non-coding RNAs (lncRNAs) and microRNAs. In recent years, a growing number of publications are available on the potential role of these molecules in health and disease [96, 97].

LncRNAs are >200 base-pairs, which can modify the structure of chromatin in the nucleus and alter gene expression [98]. It is identified that certain lncRNAs encode micro peptides that are found in the brain [99], opposing the commonly accepted term of being non-coding. LncRNAs are also associated with the circadian genes. For example, the ablation of lncRNA 116HG [100] causes dysregulation of *CLOCK*, *Cry1,* and *Per2*. In 2016, Davis et al. [101] reported differential expression

of several lncRNAs following sleep deprivation. Although the roles of lncRNAs in the diseases of the central nervous system are being clarified increasingly [102], there is no explanation regarding the associated function of these lncRNAs affected by sleep deprivation [86].

MicroRNAs are small molecules of ~22 nucleotides and are abundant in the brain, where they associate with neurological processes such as synaptic plasticity [103, 104]. MicroRNAs are also associated with sleep deprivation with mir-132 [105] and miR-138 [106] being found in sleep-deprived rats. A genome-wide study by Davis et al. [107] reported significant alterations in let-7b and miR-125a in the brain following sleep deprivation. Table 1 presents examples of altered non-coding RNAs that follow sleep deprivation.

To identify the non-coding RNAs in the epigenetic mechanisms underlying the sleep disruption in future studies, it is suggested to perform the RNA-sequencing analyses along with the validation by cloning [86].

Table 1 Examples of altered non-coding RNAs following sleep deprivation.

Study	**Outcome**	**Reference**
Sleep deprivation in mice (Male homozygous P2X7RKO mice, and wild type mice)	In wild type mice, sleep deprivation increased hypothalamic 4930470G03Rik, A230107N01Rik, C130021I20Rik, Gm17354, and decreased A430010J10Rik expression In P2X7RKO mice, sleep deprivation increased only 6820431F20 levels 2 potential lncRNA targets related to sleep were identified: 9430037G07Rik and Gm15832	Davis et al., 2016 [101]
Sleep deprivation in rats (Male Sprague-Dawley rats)	let-7b, miR-138, miR-125a are involved in sleep regulation miRNAs expression differs based on time of the day (end of dark compared with the end of light), let-7b, miR-138, miR-125a higher levels were found in pre-light onset. miRNAs expression differs based on brain region (the highest concentrations in the hippocampus, moderate in the hypothalamus, and prefrontal cortex, and lower in the occipital and somatosensory	Davis et al., 2012 [106]

	cortices)	
Sleep deprivation in rats (Male Sprague-Dawley rats)	miRNA-132 is involved in sleep regulation Spontaneous brain levels of miRNA-132 depend on brain site (hippocampus, prefrontal cortex, somatosensory cortex, and hypothalamus) and time of day miRNA-132 was highest at the prefrontal cortex and at dawn	Davis et al., 2011 [105]
Patients with major depression affected by late insomnia (359 major depression patients and 341 controls)	miR-182 is involved in insomnia miR-182 inhibits Adenylate Cyclase 6 (*ADCY6*), *CLOCK*, and *DSIP* expression; the abnormal processing of pre-miR-182 in patients carrying the T allele of the rs76481776 polymorphism may contribute to the dysregulation of circadian rhythms in these patients with insomnia	Saus et al., 2010 [108]
Sleep deprivation in mice (Male mice 57BL/6J, AKR/J, and DBA/2J)	10 miRNAs expression altered with sleep deprivation; upregulated (miR-410, −212, −29c, −29b-2, and −708) and downregulated (let-7e, miR-137, −22, −219–2, and −99a) miR-410, −212, −29c, and −151 were verified; potential targets were found for miR-151 and a tendency for miR-212	Mongrain et al., 2010 [109]
Sleep deprivation in rats (Male Sprague Dawley rats) Genome-wide study	50 miRNAs were affected by sleep loss. Let-7b and miR-125a significantly changed in all four brain regions The number of miRNAs and their expression affected by the sleep loss were brain region dependent. In hippocampus, miRNA expression	Davis et al., 2007 [107]

	increased but in somatosensory and prefrontal cortices decreased. In the hypothalamus miRNAs were both up- and down-regulated.	

2.2 Examples of the Consequences of Epigenetic Regulations in Sleep Disruption

2.2.1 Epigenetics of Sleep Disturbances and Metabolic Consequences

Chronic loss of sleep, social jet lag, and shift work are the most common reasons that are linked to an elevated risk of metabolic disorders, such as type 2 diabetes, metabolic syndrome, and obesity [110-113]. A shift in the sleep time because of weekly environmental changes or a continuous five nights of short sleep is reported to elevate the risk of weight gain in healthy individuals [113, 114]. Metabolic perturbations follow a tissue-specific pattern in peripheral tissues such as skeletal muscle and adipose tissue [115, 116]. It is also proposed that sleep loss can promote adverse catabolism and anabolism in a tissue-specific manner [117], e.g., loss of muscle mass [118, 119]. However, the underlying molecular mechanisms are less investigated. A single night of sleep loss in humans was shown to induce tissue-specific transcriptional and DNA methylation changes in circadian clock genes [88], although the downstream tissue-specific impact on metabolic pathways was not determined.

In 2018 [87], the effects of acute sleep loss were investigated on tissue-specific alterations in the metabolic pathways, i.e., anabolic versus the catabolic state. This study hypothesized that acute sleep loss would promote adipogenesis, reflecting changes in DNA methylation. Samples from subcutaneous adipose tissue and skeletal muscle were obtained from healthy young men, following a night of sleep loss and a night of full sleep, for subsequent analysis [87]. This study showed the glycolytic pathway being down-regulated in skeletal muscle but upregulated in subcutaneous adipose tissue. Transcriptomic markers of inflammation were found in both tissues, and this was the first human evidence to demonstrate that acute sleep loss may re-program DNA methylation in adipose tissue, promoting adipogenesis in adipose tissue and catabolism in skeletal muscles [87]. These observations partially explain the underlying mechanisms of weight gain and sarcopenia following the disturbance in sleep and circadian rhythm [87]. These findings were consistent with the animal studies (rats) deprived of extended REM sleep, which demonstrated atrophy in only glycolytic and mixed muscles but not in oxidative muscles [119, 120]. Insufficient sleep in middle-aged and older adults is found to be associated with lower skeletal muscle mass [111, 118]. With the presence of catabolic markers in blood and urine, loss of sleep is also observed [116, 121]. Higher catabolism following an acute sleep loss might be due to the regulatory hormonal disruptions. Cortisol, a catabolic hormone, is elevated following an acute sleep loss while testosterone [122] and nocturnal growth hormones [123] are lowered.

Changes in DNA methylation were observed in the genes that were previously demonstrated in adipose tissue of obese and type 2 diabetic patients, just after losing one night's sleep. It remains to be elucidated whether other environmental factors such as diet, exercise, and stress could modulate or alter the duration of these changes towards a worsened or rather a protective state or not [87]. A recovery sleep during the weekends, however, failed to prevent metabolic dysregulation, according to a 2019 study [124]. In this study, Depner et al. [124] evaluated sleep,

circadian timing, energy intake, weight gain, and insulin sensitivity during a period of 9 consecutive nights of insufficient sleep, followed by a weekend of ad libitum recovery sleep. Young, healthy individuals were divided into three groups: control, insufficient sleep without weekend recovery sleep, and insufficient sleep with weekend recovery sleep groups. The results presented that insufficient sleep delayed the circadian phase and increased the energy intake along with the body weight compared to the baseline. Weekend recovery sleep was not sufficient or effective in reversing the metabolic alterations caused by recurrent insufficient sleep. Also, a gender-related response was observed during the weekend recovery phase, where women showed lowered total sleep duration and a decreased energy intake of baseline levels when compared to men. This highlights the importance of including both females and males in sleep-related studies associated with epigenetic factors. In addition, this study provided evidence that the general belief of weekend recovery sleep reversing the sleep-loss alterations might not be true in normalizing the metabolic dysregulation caused by recurrent insufficient sleep [124].

Pregnancy is known as a condition in which lifestyle is transiently affected. There are numerous recommendations and guidelines available for parents to maintain maternal mental and physical health with various choices of activities, including diet, exercise, and sleep [125-128]. A majority of pregnant women experience sleep disorders, including fragmented or inadequate sleep [127, 128]. Sleep fragmentation is reported, especially during the late gestation phase [129], and sleep disorders in pregnancy were also associated with increased gestational weight gain, pregnancy complications such as gestational diabetes mellitus, and adverse perinatal and post-natal outcomes. For example, intrauterine growth restriction, low birth weight, preterm birth, a child's risk of overweight and obesity [130-132] are proposed to occur in offspring through epigenetic modifications [133]. Although some mice studies have provided evidence for the role of epigenetic factors and mediating pathways during pregnancy, there is still a lack in human studies that link gestational sleep disruption with the cardio-metabolic health of the offspring. A 2015 study demonstrated that sex dimorphism existed in mice offspring following the late gestational sleep fragmentation [134]. In this study, only the male offspring had higher food intake, body weight, visceral fat mass, insulin resistance, and lower adiponectin levels. Dyslipidemia was, however, apparent in both sexes [134]. Another study by this group investigated the effects of sleep fragmentation during late gestation on the metabolic function and expression of adiponectin in visceral white adipose tissue of the mice offspring. Male offspring of mice in the sleep fragmented group was assessed, and an increase was observed in their food intake, body weight, visceral white adipose tissue mass, and insulin resistance while adiponectin expression was reduced in the visceral white adipose tissue. Several epigenetic markers were also identified on the adiponectin found in visceral white adipose tissue of adipocytes in a male mouse offspring along with a metabolic syndrome-like phenotype. This study highlighted the importance of an altered gestational environment that can cause long-lasting metabolic consequences for future generations [135]. Later in 2016, two other mice studies [136, 137] demonstrated that gestational sleep deprivation could elevate blood pressure in offspring through the autonomic regulation in cardiovascular and renal alterations [23, 24]. A recent study in humans has evaluated the association between gestational sleep deprivation, childhood adiposity, and cardio-metabolic health [130]. Data from two European cohorts were used to accommodate diversity in ethnic and demographic characteristics, and it was found that gestational sleep deprivation might be associated with an increased risk of overweight and higher blood pressure in offspring till the age

of 11 years [130]. This study also showed that the association was more pronounced in girls than boys [130], which is in contrast with mice study. Along with sleep deprivation, the authors of this study also encourage further studies on sleep quality during pregnancy [130]. Also, there is a need for an official sleep recommendation for pregnant women; however, based on the findings of this study, sleep deprivation (i.e., sleep duration of 6 h and less) has to be avoided at any stage of pregnancy [130].

2.2.2 Sleep Deprivation Alters Brain and Blood Phenome

Analysis of both animal and selected human samples have provided evidence that sleep deprivation alters the transcriptome and methylome [42, 43, 88, 138-140]. In rats, sleep deprivation altered the brain transcriptome affecting protein synthesis, synaptic plasticity, and metabolism [138, 141]. Archer et al. [142] presented that mistiming sleep could reduce rhythmic transcripts and cause remarkable alterations in the transcriptome. The average methylation in the night-shift workers was significantly reduced compared to the dayshift workers [143, 144]. This implies that underlying mechanisms with negative consequences of chronic lack of sleep need greater attention towards the night-shift workers. Genetic risk factors are also reported in people having an intolerance towards shift work [145] and an association was found between job-related exhaustion and a variant of the melatonin receptor 1A gene, proposing that the mechanism of changes in DNA methylation at the gene promoter are in response to the shift work [145]. In light of the value of studying DNA methylation for understanding mechanisms underlying insomnia, in 2019, Lahtinen et al. [146] investigated blood leukocytes to identify differentially methylated DNA in samples obtained from DILGOM, a sub-study of the population-based FINRISK along with a population that consisted of airline shift workers. This cross-sectional, genome-wide study identified a remarkable low level of DNA methylation (hypomethylation) in both cohorts associated with sleep loss [146]. A distinctive pattern was observed in individuals having sleep disturbances, where 399 differentially methylated positions were identified, out of which 327 were linked to the nervous system development pathway, which is also in line with the previous data, where DNA methylation induced by sleep disturbances was involved in synaptic plasticity and neuritogenesis [42]. It is worth mentioning that previous studies have analyzed DNA methylation in the brain tissue of rodents, whereas Lahtinen et al. [146] revealed these systemic changes in response to sleep disturbances in human blood samples. This shows that it is important to consider systemic sleep disturbance effects while selecting the right choice of sample for analysis.

Future studies must consider racial and ethnic disparities while designing epigenetic studies regarding sleep and sleep disruptions. An association analysis study consisting of a racially diverse population [147] measured DNA methylation in monocytes to identify whether a link exists between these markers and daytime sleepiness, and it was found that most significant DNA methylation was specific to African Americans [147].

2.2.3 Irregular or Shorter Sleep Accelerates Epigenetic Aging

A recent pilot study by Carskadon et al. [148] in young females identified that shorter or irregular sleep might advance epigenetic aging. In this study, 12 young women, defined as short or long sleepers, were studied for nine weeks. Blood samples were obtained to determine the effects

of DNA methylation levels on epigenetic age. The results revealed that longer and regularly sleeping females had a lesser difference between their chronological and epigenetic age compared to those with shorter and irregular sleep. Thus, poor sleep was found to be associated with a marked acceleration of epigenetic aging [148]. Regular meditation has been suggested to slow down the epigenetic aging [149]. Also, exercise reduces DNA methylation at age-related CpG sites [150, 151], highlighting the value of studies on behavioral interventions in epigenetic mechanisms. This is particularly an interesting area since a review from 2018 [152] had discussed the potentials of epigenetic regulation of the adult dentate gyrus (DG) neurogenesis and the influence of sleep and epigenetic modifications on this neurogenesis. Evidence shows that cognitive and emotional processing and memory consolidation are affected by the neurogenesis, thereby suggesting ways to use sleep or epigenetic interventions as therapies for neurodegenerative and psychiatric disorders [152]. In light of the growing population of aged people and the prevalence of neurodegenerative and neuropsychiatric disorders in our societies, studying sleep-related neural processes and epigenetic mechanisms may facilitate novel approaches to prevent and treat these disorders.

2.2.4 Role of Epigenetic Regulations in Sleep under the Influence of Other Lifestyle Factors

Sleep is influenced by several other lifestyle factors [153], including diet, exercise, smoking, and medications. Further research is needed to understand the mechanisms underlying the effects of all these factors. The effects of diet are more commonly studied among these factors. High carbohydrate diets, along with the foods containing tryptophan, melatonin, and phytonutrients (e.g., cherries) were linked to improving sleep outcomes [154]. This effect is proposed to be exerted through serotonin and melatonin. Also, it is reported that after short-term sleep deprivation, melatonin can promote the proliferation of neural stem cells in the adult hippocampus, where evidence indicates that epigenetic regulators may be involved. A recent study [155] investigated the effect of melatonin treatment on a 96-hour sleep-deprived subject and analyzed the expression of epigenetic modulators. The results showed that the administration of melatonin under sleep-deprived conditions increased *MECP2* expression but reduced *SIRT1* expression in DG. Let-7b, mir-132, and mir-124 were highly expressed upon the administration of melatonin but were not modified by sleep deprivation. In the subgranular zone of the sleep-deprived group treated with melatonin, more number of Sox2+/5-Bromo-2'-deoxyuridine (BrdU)+ cells were identified compared to the untreated group. These findings may support the notion that melatonin modifies the expression of epigenetic mediators, which in turn regulates the proliferation of neural progenitor cells in the adult DG under long-term sleep-deprived conditions. However, sleep-melatonin and its interaction with epigenetic factors need further investigation.

Coffee is a commonly consumed drink and is widely discussed for its related risks and benefits in health [156]. For example, heavy consumption of coffee can induce insomnia [156], and caffeine is known to reverse the negative effects of sleep deprivation while promoting prolonged wakefulness [157, 158]. Caffeine blocks adenosine from binding to its receptor, resulting in improved cognitive function and increased alertness [159, 160]. DNA methylation is proposed to play a role in caffeine-health interaction [161]. Epigenetic studies of caffeine were mainly reported in animals [162-164], while the first study in humans was conducted by Chuang et al. in 2017 [165]

to investigate whether coffee consumption induced epigenetic changes in humans. The results of this study suggested that coffee affected DNA methylation levels in blood immune cells [165]. Many of the differentially methylated CpGs related to coffee consumption were located in or near the genes that were associated with coffee-related chronic diseases, including the neurodegenerative diseases (e.g., Parkinson's Disease and Alzheimer disease). Interestingly, coffee is also known to be beneficial for these neurodegenerative disorders [166, 167]. However, one must consider that the study by Chuang et al. [165] included mixed race and gender and did not particularly focus on sleep. Therefore, the effects of caffeine on epigenetic modifications of sleep would need further investigation.

Other dietary components were also proposed to alter epigenetic pathways that might have potentially interacted with sleep. For example, dietary methyl donors (e.g., folate and choline) were proposed to promote DNA methylation and, in turn, increased promoter methylation was associated with transcriptional suppression [168]. Based on this, "epigenetic diets", were also proposed [169], but these diets were questionable since the term epigenetic diet was used for the diet, which was folate-rich as well [170].

Dietary components were also proposed to influence histone modification [171]. Gut-brain axis and bidirectional cross-talk were being investigated extensively in many human health conditions [153]. A diverse range of methods was applied to modulate the gut microbiome, including antibiotic therapy, fecal microbiota transplant, or dietary intervention, such as the use of probiotics [172]. Probiotics have shown promising results in many conditions, such as neurodegenerative disorders [173] and migraine [174]. Dietary factors can modify the gut microbiome through epigenetic pathways [175], and this might be applicable to sleep disorders as well.

Omic studies can be employed to investigate transcriptomics, proteomics, and metabolomics of sleep-diet interactions. Changes in the DNA methylation patterns, histone modifications, and regulatory RNA transcriptomics would broaden the spectrum to characterize and understand the complicated interaction between sleep and other lifestyle factors such as diet, in light of epigenetics, and this will eventually lead to a personalized medicine strategy [176]. However, this is challenging because multiple lifestyle factors are concurrently being tested. Epigenetics is also involved in a wide range of processes and can facilitate better adaptation to environmental factors and is not always associated with a negative outcome. Therefore, understanding how to modulate the epigenetic-related factors optimally may prove beneficial in coping and adaptative methods.

3. Future Perspectives

Studying epigenetic mechanisms of sleep disruption and its reversal is a fascinating and growing field, yet it is complicated and challenging to deal with. Although few studies have elucidated the roles and the epigenetic mechanisms of sleep disruption to some extent, our review positively provides the evidence for these as well. Further investigation of functional interactions between epigenetic factors and sleep disorders would help in understanding the nature of the interaction. It is desirable to understand if the interactions are causal, modulatory, or correlative. Along with the identification of epigenetic factors influencing sleep, we also need to consider investigations that focus on recovery or prevention of these alterations to restore the balance or normalize sleep disturbances. We need evidence provided by further research in a

diverse range of models with different conditions related to the neurobiology of sleep, to identify whether epigenetic mechanisms, such as DNA methylation, are disturbed in such cases and if blocking the DNA methylation can reverse the condition. Interventions might range from simple modification strategies such as recovery sleep, diet, exercise to multidimensional or integrated strategies that include medications, coping, and adaptation strategies. However, one must also consider counterbalance risk and safety issues of modification strategies. Most experimental studies in humans and animals focus on acute controlled conditions, which are highly valuable, but chronic sleep alterations and reversal strategies may show a different pattern on the epigenome. Also, most studies focus on sleep loss, whereas sleepiness studies are equally important. Interestingly, some small changes in sleep may lead to unexpected epigenetic alterations, which are important to consider in study designs. For example, changes in the length of the day may influence the pattern of DNA methylation. Azzi et al. [177] kept mice under a day length of 22-hour and 24-hour, and this small change of 2-hour difference revealed alterations in methylation patterns at promoter regions of *SCN*, leading to changes in gene expression. This supports the idea that DNA methylation might be a sensitive and rapidly occurring process. These alterations were, however, reversed when a cycle of 24-hour was extended over two weeks in this study [177], highlighting that DNA methylation might serve as an adaptive process that can be adjusted to environmental conditions, such as altered day length. Therefore, it can be assumed that DNA methylation might be beneficial in body coping strategies. This is an interesting finding as people living far north may show different patterns of DNA methylation at baseline levels and also be differentially affected in response to circadian changes.

Epigenetics can also be explored to help in the diagnosis or stratification of patients, where the expression of epigenetic markers in insomnia or sleepiness could be used as diagnostic criteria. These markers can also help with the optimal choice of pharmacological or non-pharmacological interventions [80]. If further evidence confirms a relationship between epigenetic changes and sleep disorders, then stimulation or inhibition of epigenetic markers may offer a novel strategy for the treatment or prevention of sleep disorders, which is valuable because current strategies applied in sleep disturbances [178-180] are only partially effective or carry side effects. Also, sleep disturbances are often comorbid, and this complexity makes therapeutic management even more challenging [80].

Omics have proved useful in studying many health-related conditions, such as cancer, metabolic disorders, or pain [181-183]. Integrative omic systems (genomics, proteomics, or metabolomics) would be beneficial in studying epigenetic mechanisms underlying sleep disruption, as it allows us to study the expression of markers at different interactive levels. In order to analyze the consequences of environmental influence [184], potential sleep-disturbing factors, such as high work demands, light exposure, job strain, noise, and shift schedules can be considered [185-187]. Isolated and integrated lifestyle factors related to epigenetics can bring new insight into interacting factors (such as diet, exercise, smoking, and stress) since they are unavoidable in real-life conditions.

Animal models have provided useful information on molecular mechanisms of sleep disorders, including narcolepsy, sleep apnea, restless legs syndrome, and insomnia [39]. DNA methylation, histone modifications, chromatin remodeling, non-coding RNA regulation, and RNA editing can be studied in these models [188, 189]. However, the translatability of this data to humans must be considered carefully with factors such as race, sex, comorbid disorders, and concomitant

medications, which can lead to proper designing of future studies. Hence, multimodal assessment and correlation analysis of objective and subjective markers related to sleep can enrich our understanding of underlying mechanisms and complexity of targeting. Also, different epigenetic elements must be considered to design future studies.

Considering the limited but promising findings and several open research avenues in this field, it is highly expected to witness rapidly emerging studies and evidence generation in the coming years on the role and significance of epigenetic regulation in sleep disruptions. Epigenetic studies for sleep disorders will not only enhance our understanding of the risks but also help in recognizing the importance of various environmental factors influencing the sleep disorders, and eventually modulating these factors may further help us in treating patients and providing preventive strategies.

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